a method of immunizing a mammal (claims 26-32), and a pharmaceutical composition comprising a complex and a physiologically-acceptable carrier (claims 40, and 43-51).

Discussion of Office Action

Claims 3-32 and 40-43 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. Claims 1, 2, 4-7, 9, 11-16, 19, 26, 27, 40, 42, and 43 also are rejected under 35 U.S.C. § 102(b), and claims 8, 10, 18, 20-23, 25, 28-30, 32, and 41 are rejected 103(a) on the basis of cited references.

Discussion of Amendments

The specification is amended to properly indicate that the RGD ligand binds cell surface integrin, rather than heparin. This subject matter is supported in the specification, for example, on page 3, line 30. The principle also is known in the art (see, e.g., Wickham et al., *Cell, 73*(2):309-19 (1993) (attached)).

Claim 1 is amended to state that the complex has at least one non-native second antigen displayed on the surface of the virion. This amendment is supported in the specification, for example, on page 6, line 35, through page 7, line 9 and by original claim 7, which is canceled. Claims 8 and 9 are amended to depend from claim 1, rather than canceled claim 7.

Claim 26 is amended to more distinctly claim the invention by reciting that the second non-native antigen is displayed on the surface of the virion. This amendment is supported in the specification, for example, on page 6, line 35, through page 7, line 9.

Claim 40 is amended to depend from claim 1.

New claims 44-51 are added to more distinctly claim the polypeptide recited in their respective antecedent claims. This subject matter is supported in the specification, for example, on page 9, lines 15-20, and by original claims 17, 18, 24, 25, 31, and 32.

The amendments add no new matter to the application. For the convenience of the Examiner, a printout of the amended specification page and the claims, indicating the language added and removed, is attached. Furthermore, a separate printout indicating the text of all claims pending upon entry of this amendment is also attached.

Discussion of Enablement Rejection

Claims 3-32 and 40-43 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. This rejection is based on the Office Action's assertion that the role of CD40 ligand and osteopontin is unclear. As a threshold matter, it should be noted that only claims 3, 17, 24, and 31 (and new claims 44 and 46-51) recite CD40 ligand or

osteopontin, and no claims are dependent on these claims. Thus, it is urged that the rejection should only apply to these claims, rather than claims 3-32 and 40-43, as stated in the Office Action.

In any event, applicants urge that the specification, in combination with the state of the art, fully enables the invention as recited by all pending claims. The prior Office Action suggested that the CD-40 ligand depresses the immune system and that the state of the art did not recognize the role of osteopontin (Office Action, page 2, citing Stein et al. and Yu et al.). In response, applicants had noted that references of record (Ashkar et al. and Toes et al.) demonstrated the immunoactive role of these two proteins. Herewith, applicants submit additional references further demonstrating that the state of the art recognizes the immunostimulatory activity of osteopontin (Attur et al., *Arthrit. Rheum.*, 44(3), 578-84 (2001); Carlson et al., *Lab. Invest.*, *77*(1), 103-108 (1997); Denhardt et al., *Ann. Rev. Pharmacol. Toxicol.*, *41*, 723-49 (2001); Nagal et al., *Int. Immunol.*, *13*(3), 367-76 (2001); O'Regan et al., *J. Leuk. Biol.*, *68*, 495-502 (2000); O'Regan et al., *J. Exp., Path.*, *81*, 373-90 (2000); O'Regan et al., *Immunol. Today, 21*(10) 475-78 (2000); Shijubo et al., *Crit. Rev. Oncogen.*, *11*(2), 135-46 (2000); O'Regan et al., *J. Immunol.*, *162*(2), 1024-31 (1999); Rittling et al., *Exp. Nephrol.*, *7*, 103-113 (1999); Weber et al., *Cytokine Growth Factor Rev.*, *7*(3), 41-48 (1996) (attached)). Moreover, additional work aptly demonstrates that transfer of a gene encoding CD40 ligand, particularly using viral-based gene transfer technology, can exert powerful immunostimulatory action *in vivo* (see, e.g., Kikuchi et al., *Hum. Gene Ther.*, *12*(10):1251-63 (2001); Kikuchi et al., *Blood, 96*(1), 91-99 (2000); Kikuchi et al., *Cancer Res.*, *60*(22), 6391-95 (2000); Kikuchi et al., *Nature Med.*, *6*(10), 1154-59 (2000); Kikuchi et al., *Hum. Gene Ther.*, *10*(8):1375-87 (1999) (attached)). From such references, one of skill in the art would understand that both CD40-L and osteopontin can be used to augment immunoactivation. It is therefore urged that all claims are enabled, and applicants request withdrawal of the rejection under Section 112.

Discussion of Anticipation Rejection

Claims 1, 2, 4-7, 9, 11-16, 19, 26, 27, 40, 42, and 43 are rejected under 35 U.S.C. § 102(2) as allegedly anticipated by Wickham et al. (U.S. Patent 5,846,782). The Office Action states that the "passenger gene" discussed in Wickham could encode an antigen. Applicants maintain that the teachings of Wickham et al do not inherently anticipate the original claims. However, even if the "passenger gene" discussed in Wickham et al., if antigenic, could be argued to be the encoded "first antigen" of the present invention, Wickham et al. does not disclose a virus including both (a) a nucleic acid encoding a first

non-native antigen, and (b) a second non-native antigen displayed on the surface of the viral capsid. The complexes of amended claims 1 and 26 have both encoded and displayed antigens, and all claims depend ultimately from claims 1 or 26. As such, all claims are novel in light of Wickham et al., and the rejection under Section 102 should be withdrawn.

Discussion of Obviousness Rejection

Claims 8 and 10 are rejected as allegedly obvious over the combination of Wickham et al. and Hitt et al., and claims 18, (20)21-23, 25, 28-30, 32 (and 41) are alleged to be obvious in light of these two references combined with Janeway. As stated above in connection with the discussion of anticipation, the Wickham et al. patent does not provide a teaching sufficient to place the elements of claims 1 and 26 (upon which all other claims depend) in the art. Thus, its contribution to the proffered combination for obviousness purposes is insufficient to disclose needed elements of the claims. For this reason alone, the obviousness rejection should be withdrawn. The two proffered combinations of references will be further discussed separately below.

Wickham et al. and Hitt et al. – claims 8-10

For the combination of references to render the claims obvious, (1) the references must disclose all elements of the claimed invention, (2) there must be evidence of some teaching or suggestion to make the proffered combination, and (3) there must exist a reasonable expectation of success arising from the proffered combination. The teaching of Wickham et al. is to redirect adenoviral tropism using non-native ligands displayed on the surface of the adenoviral capsid. Hitt et al. disclose methods for human adenovirus vector construction. However, neither Hitt et al. nor Wickham et al make any reference to any vector having two antigens (e.g., one encoded in the adenoviral genome, the other on the surface of the virus), and certainly not wherein the first and second antigens are the same. Thus, neither Hitt et al. nor Wickham et al. place the elements of claims 8 or 10 in the art. For this reason alone, the rejection should be withdrawn.

Applicants have stated that the previous Office Action had not provided evidence of any motivation to combine these references. Of course, the Office must provide "objective evidence" of such motivation (MPEP § 2143.01). However, the present Office Action states merely that "one of skill in the art at the time the invention was made would have been motivated" to make the combination. Such "***broad conclusory statements standing alone are not 'evidence'***" sufficient to support an obviousness conclusion. *In Re Kotzab*, 217 F.3d 1365, 55 U.S.P.Q.2d 1313 (Fed. Cir. 2000). Instead, to support an

obviousness conclusion, "***particular findings must be made as to the reason*** the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." (*Id.*). The Office Action simply fails to meet this standard, and, as such, it has not established *prima facie* obviousness. In fact, nothing in either cited reference suggests such a combination, nor does the art as a whole. For this second reason – i.e., absence of any motivation to make the combination – the rejection should be withdrawn as to claims 8 and 10.

Wickham et al., Hitt et al, Janeway et al. – claims 18, 21-23, 25, 28-30, and 32

The teachings of Wickham et al. and Hitt et al. are stated above. Also presented above are applicants arguments that (1) neither alone nor in combination do Wickham et al. and/or Hitt et al. disclose the elements of the antecedents to the rejected claims and (2) there is no motivation to combine the teachings of Wickham et al. and Hitt et al. These reasons apply equally to the combination of Wickham et al., Hitt et al, and Janeway et al., and for any of these reasons the rejection of claims 18, 21-23, 25, 28-30, and 32 should be withdrawn.

The previous Office Action noted that the Janeway et al. teaches that IFNγ augments MHC I and II responses. However, the Office Action fails to present any ***objective*** evidence that one of skill in the art would be motivated to combine the teachings of these three references in any manner, much less in the manner needed to arrive at the claimed invention (which, in any event, is not possible because the elements of the claimed invention is not present in the three references). Absent any objective evidence of this motivation, *prima facie* obviousness has not been demonstrated. In fact, neither Janeway, nor Hitt et al., nor Wickham et al. provides any teaching to complex nucleic acid encoding a cytokine - not even IFNγ - with anything else, and certainly not a viral vector having an encoded and a displayed antigen. Thus, the art supplies absolutely no motivation whatsoever to combine the teachings of these references to arrive at the invention recited in the rejected claims. As such, the rejection of claims 18, 21-23, 25, 28-30, and 32 under Section 103 should be withdrawn.

Conclusion

The application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the examination of the instant application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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